

**Amendments to the Specification:**

Please replace the title beginning at page 1, line 1, with the following:

--FACTOR IX/FACTOR ~~IXa~~ IXa ACTIVATING ANTIBODIES  
AND ANTIBODY DERIVATIVES--

Please replace the paragraph beginning at page 6, line 23, with the following:

--Fig. 12 shows the primer sequences (SEQ ID NOS:50-61)  
for the amplification of the genes of the variable heavy  
chain of mouse antibody.--

Please replace the paragraph beginning at page 6, line 26, with the following:

--Fig. 13 shows the primer sequences (SEQ ID NOS:65-78)  
for the amplification of the genes of the variable light  
(kappa) chain of the mouse antibody.--

Please replace the paragraph beginning at page 9, line 13, with the following:

--Fig. 32 shows a schematic representation of the  
plasmid pMyHis6 (SEQ ID NOS:107-110).--

Please replace the paragraph beginning at page 36, line 14, with the following:

--The coding sequences for VH were amplified by PCR  
using the primer-sets depicted in Fig. 12 and the specific

cDNA, derived from the reverse transcription mixture (RTmix1) described above, as the template. VK-chain genes were amplified using the primer sets depicted in Fig. 13 and also employing Rtmix1 as a template. The VH-PCR product was cleaved SfiI-AscI and inserted into SfiI-AscI digested vector pDAP2 (GeneBank accession no.: U35316). The pDAP2-VH constructs obtained thereby were named pDAP2-193AD3/VH, pDAP2-198A1/VH, pDAP2-198AB2/VH (derived from antibody 198/B1) and pDAP2-193/K2/VH, respectively. The plasmids were subsequently cleaved with AscI-NotI and the corresponding AscI-NotI digested VK-gene PCR product was inserted. The resultant vectors were designated pDAP2-193/AD3scFv, pDAP2-198/A1scFv, pDAP2-198/AB2scFv (derived from antibody 198/B1) and pDAP2-193/K2scFv and code for the VH-gene and the VL-gene of the monoclonal antibodies 193/AD3, 198/A1, 198/AB2 (derived from antibody 198/B1) and 193/K2. Heavy and light chains are linked by the coding sequence for an artificial, flexible linker (G<sub>4</sub>SGGRASG<sub>4</sub>S (SEQ ID NO:111); Engelhardt et al., 1994) and enables expression of the scFv variant of the respective antibody.--

Please replace the paragraph beginning at page 37, line 1, with the following:

--In Fig. 14, the DNA and the deduced protein sequence of the scFv derived from the hybridoma cell line 193/AD3 are depicted. Nucleotides 1 to 357 code for the heavy chain variable domain, nucleotides 358 to 402 code for the artificial flexible linker and nucleotides 403 to 726 code for the light chain variable region. The protein sequence

of the CDR3 region of the heavy chain has the sequence  
YGNSPKGFAY ~~(SEQ.ID.NO. 5)~~ (SEQ ID NO:5) and is given in  
bold letters. The artificial linker sequence (G<sub>4</sub>SGGRASG<sub>4</sub>S;  
SEQ ID NO:111) is shown.--

Please replace the paragraph beginning at page 37, line 11, with the following:

--In Fig. 15, the DNA and the deduced protein sequence  
of the scFv derived from the hybridoma cell line 193/K2 is  
shown. Nucleotides 1 to 363 code for the heavy chain  
variable domain, nucleotides 364 to 408 code for the  
artificial flexible linker, and nucleotides 409 to 747 code  
for the light chain variable region. The protein sequence  
of the CDR3 of the heavy chain has the sequence  
DGGHGYGSSFDY ~~(SEQ.ID.NO. 6)~~ (SEQ ID NO:6), and is given in  
bold letters. The artificial linker sequence (G<sub>4</sub>SGGRASG<sub>4</sub>S;  
SEQ ID NO:111) is ~~show~~ shown.--

Please replace the paragraph beginning at page 37, line 21, with the following:

--In Fig. 16, the DNA and the deduced protein sequence  
of the scFv derived from the hybridoma cell line 198/AB2  
(derived from antibody 198/B1) are depicted. Nucleotides 1  
to 366 code for the heavy chain variable domain,  
nucleotides 367 to 411 code for the artificial flexible  
linker, and nucleotides 412-747 code for the light chain  
variable region. The protein sequence of the CDR3 region of  
the heavy chain has the sequence EGGGFTVNWYFDV ~~(SEQ.ID.NO. 7)~~  
(SEQ ID NO:7) and is given in bold letters. The

SCHEIFLINGER *et al.*  
Application No.: 09/661,992  
Page 6

PATENT

artificial linker sequence (G<sub>4</sub>SGGRASG<sub>4</sub>S; SEQ ID NO:111) is  
also shown.--

Please replace the paragraph beginning at page 37, line 32, with the following:

--In Fig. 17, the DNA and the deduced protein sequence of the scFv derived from the hybridoma cell line 198/A1 are depicted. Nucleotides 1 to 366 code for the heavy chain variable domain, nucleotides 367 to 411 code for an artificial flexible linker, and nucleotides 412-747 code for the light chain variable region. The protein sequence of the CDR3 region of the heavy chain has the sequence EGGGYVNWYFDV ~~(SEQ.ID.NO.8)~~ (SEQ ID NO:8) and is given in bold letters. The artificial linker sequence (G<sub>4</sub>SGGRASG<sub>4</sub>S;  
SEQ ID NO:111) is also shown.--

Please replace the paragraph beginning at page 39, line 27, with the following:

--The principle of such a study is exemplified by a series of peptides derived from CDR3<sub>H</sub> region of antibodies 198/A1 and 198/B1. The original peptide A1 (see table 2) is derived from the CDR3<sub>H</sub> region of antibody 198/A1 and peptide B1 is derived from the CDR3<sub>H</sub> region of antibody 198/B1, respectively (see example 10, Fig. 16 and 17). The term "scrambled version" means that a peptide has the same amino acids but in random order.

Peptide	Sequence	Amino-acids	MW (D)	pI	Remark
A1	EGGGYYVNWYFDV (SEQ. ID. No. 9) (SEQ ID NO:8)	(13aa)	1569	7.2	Decreased solubility
A1/1	VYGFGWGYEVNDY (SEQ. ID. No. 10) (SEQ ID NO:10)	(13aa)	1569	7.1	Scrambled version of A1,
A1/2	EEEEGGGYVNWYFDEEE (SEQ. ID. No. 11) (SEQ ID NO:11)	(18aa)	2244	5.8	Acidic pI, soluble,
A1/3	RRREGGGYYVNWYFDRRR (SEQ. ID. No. 12) (SEQ ID NO:12)	(18aa)	2407	9.9	Basic pI, soluble,
A1/4	EYGEYGEVNEYDEFWE (SEQ. ID. No. 13) (SEQ ID NO:13)	(18aa)	2244	5.8	Scrambled version of A1/2
A1/5	VRYNRYRWGYRGRFGDE (SEQ. ID. No. 14) (SEQ ID NO:14)	(18aa)	2407	9.9	Scrambled version of A1/3
A1/3-scr3	RRRGEYGVYWNGDFYRRR (SEQ. ID. No. 15) (SEQ ID NO:15)	(18aa)	2407	9.9	Scrambled version of A1/3
A1/3-Rd	RdRdRdEGGGYYVNWYFDRdRdRd (SEQ. ID. No. 16)	(18aa)	2407	9.9	Peptide A1/3 but substitute D-Arg for L-Arg
A1/3-Rd-srmb	RdRdRdGEYGVYWNGDFYRdRdRd (SEQ. ID. No. 17)	(18aa)	2407	9.9	Scrambled version of A1/3-Rd

Table 2

List of a series of antibody 198/A1 derived peptides.  
Listed are the length of the peptide (aa, amino acids #),  
the calculated molecular weight (MW, in Dalton (D) and the  
statistical isoelectric point (pI). D-Arg is abbreviated as  
Rd.--

Please replace the paragraph beginning at page 40, line 9, with the following:

--In a first series of experiments we improved the solubility of the original CDR3<sub>H</sub> peptide sequence (A1; EGGGYVNWYFDV; SEQ ID NO:8) by removing the C-terminal Val residue and adding several charged residues at the N- as well as the C-terminal end of the peptide. The resulting peptides, A1/2 (acidic pI), A1/3 (basic pI) and their respective scrambled versions A1/4, A1/5 and A1/3scr3 were readily soluble in a variety of buffer systems at physiological pH.--

Please replace the paragraph beginning at page 46, line 10, with the following:

--In the next series of experiments we set out to determine the individual role of any amino acid of the peptide core sequence by substituting each residue for the amino acid Alanine (Table 5).

Peptide	Sequence	Amino acid #	MW (D)	pI	Remark
A1/3	RRREGGGYYVNWYFDRRR ( <del>SEQ. ID. No. 18</del> ) (SEQ ID NO:12)	(18aa)	2407	9.9	Basic pI, soluble,
A1/3-13	RRR <b>A</b> GGGYVNWYFDRRR (SEQ. ID. No. 19) (SEQ ID NO:19)	(18aa)	2349	10.4	E <sub>1</sub> -A <sub>1</sub>
A1/3-1	RRRE <b>A</b> GGYYVNWYFDRRR ( <del>SEQ. ID. No. 20</del> ) (SEQ ID NO:20)	(18aa)	2421	9.9	G <sub>2</sub> -A <sub>2</sub>
A1/3-2	RRREG <b>A</b> GYYVNWYFDRRR ( <del>SEQ. ID. No. 21</del> ) (SEQ ID NO:21)	(18aa)	2421	9.9	G <sub>3</sub> -A <sub>3</sub>
A1/3-3	RRREGG <b>A</b> YYVNWYFDRRR ( <del>SEQ. ID. No. 22</del> ) (SEQ ID NO:22)	(18aa)	2421	9.9	G <sub>4</sub> -A <sub>4</sub>
A1/3-4	RRREGGG <b>A</b> YVNWYFDRRR ( <del>SEQ. ID. No. 23</del> ) (SEQ ID NO:23)	(18aa)	2315	9.9	Y <sub>5</sub> -A <sub>5</sub>
A1/3-5	RRREGGGY <b>A</b> VNWYFDRRR ( <del>SEQ. ID. No. 24</del> ) (SEQ ID NO:24)	(18aa)	2315	9.9	Y <sub>6</sub> -A <sub>6</sub>
A1/3-6	RRREGGGYY <b>A</b> NWYFDRRR ( <del>SEQ. ID. No. 25</del> ) (SEQ ID NO:25)	(18aa)	2379	9.9	V <sub>7</sub> -A <sub>7</sub>
A1/3-7	RRREGGGYYV <b>A</b> WYFDRRR ( <del>SEQ. ID. No. 26</del> ) (SEQ ID NO:26)	(18aa)	2364	9.9	N <sub>8</sub> -A <sub>8</sub>
A1/3-8	RRREGGGYYVN <b>A</b> YFDRRR ( <del>SEQ. ID. No. 27</del> ) (SEQ ID NO:27)	(18aa)	2292	9.9	W <sub>9</sub> -A <sub>9</sub>
A1/3-9	RRREGGGYYVNW <b>A</b> FD ( <del>SEQ. ID. No. 28</del> ) (SEQ ID NO:28)	(18aa)	2315	9.9	Y <sub>10</sub> -A <sub>10</sub>
A1/3-10	RRREGGGYYVNWY <b>A</b> DRRR ( <del>SEQ. ID. No. 29</del> ) (SEQ ID NO:29)	(18aa)	2331	9.9	F <sub>11</sub> -A <sub>11</sub>
A1/3-11	RRREGGGYYVNWYF <b>A</b> RRR ( <del>SEQ. ID. No. 30</del> ) (SEQ ID NO:30)	(18aa)	2363	10.5	D <sub>12</sub> -A <sub>12</sub>
A1/3-12srmb	RRRYVYNGWGYFEG <b>A</b> RRR ( <del>SEQ. ID. No. 31</del> ) (SEQ ID NO:31)	(18aa)	2363	10.4	Scrambled version

Table 5. Listed are the peptides designed to elucidate the role of any single amino acid within the peptide core sequence (E<sub>1</sub>G<sub>2</sub>G<sub>3</sub>G<sub>4</sub>Y<sub>5</sub>Y<sub>6</sub>V<sub>7</sub>N<sub>8</sub>W<sub>9</sub>Y<sub>10</sub>F<sub>11</sub>D<sub>12</sub>; SEQ ID NO:112). The lower



ease subscripted numbers describe the position of the amino acid within the peptide. Alanine, an uncharged small amino acid, was substituted for each amino acid ("Alanine scan"). Also listed are the lengths of the peptides (amino acids #), the calculated molecular weights (MW, in Dalton (D) and the statistical isoelectric points (pI).--

Please replace the paragraph beginning at page 47, line 35, with the following:

--In the next series of experiments we set out to determine the individual role of any amino acid of the peptide core sequence by substituting each core residue for the amino acid glutamic acid (E) (see Table 6).

Peptide	Sequence	Amino-Acids	MW (D)	pI	Remark
A1/3	RRREGGGYYVNWYFDRRR (SEQ ID NO:12)	(18aa)	2407	9.9	Basic pI, soluble,
A1/3-22	RRREGGGYYVNWYFDRRR ( <del>SEQ ID No. 32</del> ) (SEQ ID NO:32)	(18aa)	2479	9.5	G <sub>2</sub> -E <sub>2</sub>
A1/3-23	RRREGGGYYVNWYFDRRR ( <del>SEQ ID No. 33</del> ) (SEQ ID NO:33)	(18aa)	2479	9.5	G <sub>3</sub> -E <sub>3</sub>
A1/3-24	RRREGGGYYVNWYFDRRR ( <del>SEQ ID No. 34</del> ) (SEQ ID NO:34)	(18aa)	2479	9.5	G <sub>4</sub> -E <sub>4</sub>
A1/3-26	RRREGGGYYVNWYFDRRR ( <del>SEQ ID No. 35</del> ) (SEQ ID NO:35)	(18aa)	2373	9.4	Y <sub>5</sub> -E <sub>5</sub>
A1/3-27	RRREGGGYYVNWYFDRRR ( <del>SEQ ID No. 36</del> ) (SEQ ID NO:36)	(18aa)	2373	9.4	Y <sub>6</sub> -E <sub>6</sub>
A1/3-28	RRREGGGYYVNWYFDRRR ( <del>SEQ ID No. 37</del> ) (SEQ ID NO:37)	(18aa)	2437	9.5	V <sub>7</sub> -E <sub>7</sub>
A1/3-29	RRREGGGYYVNWYFDRRR ( <del>SEQ ID No. 38</del> ) (SEQ ID NO:38)	(18aa)	2422	9.5	N <sub>8</sub> -E <sub>8</sub>
A1/3-30	RRREGGGYYVNWYFDRRR ( <del>SEQ ID No. 39</del> ) (SEQ ID NO:39)	(18aa)	2350	9.5	W <sub>9</sub> -E <sub>9</sub>
A1/3-31	RRREGGGYYVNWYFDRRR ( <del>SEQ ID No. 40</del> ) (SEQ ID NO:40)	(18aa)	2373	9.4	Y <sub>10</sub> -E <sub>10</sub>
A1/3-32	RRREGGGYYVNWYFDRRR ( <del>SEQ ID No. 41</del> ) (SEQ ID NO:41)	(18aa)	2389	9.5	F <sub>11</sub> -E <sub>11</sub>
A1/3-33	RRREGGGYYVNWYFDRRR ( <del>SEQ ID No. 42</del> ) (SEQ ID NO:42)	(18aa)	2421	9.9	D <sub>12</sub> -E <sub>12</sub>
A1/3-34srm	RRREGGEYVWNGDFYRRR ( <del>SEQ ID No. 43</del> ) (SEQ ID NO:43)	(18aa)	2437	9.5	Scrambled version

Table 6. Listed are the peptides designed to elucidate the role of any single amino acid within the peptide core sequence (E<sub>1</sub>G<sub>2</sub>G<sub>3</sub>G<sub>4</sub>Y<sub>5</sub>Y<sub>6</sub>V<sub>7</sub>N<sub>8</sub>W<sub>9</sub>Y<sub>10</sub>F<sub>11</sub>D<sub>12</sub>; SEQ ID NO:112). The lower case subscripted numbers describe the position of the amino acid within the peptide. Glutamic acid, a negatively

charged large amino acid, was substituted for each amino acid of the core sequence ("Glutamic acid scan"). Also listed are the lengths of the peptide (amino acids #), the calculated molecular weights (MW, in Dalton (D) and the statistical isoelectric points (pI).--

Please replace the paragraph beginning at page 49, line 14, with the following:

--In a second series of experiments we set out to improve the procoagulant activity of the antibody 198/B1 CDR3H derived peptide sequence B1. In a first step we improved the solubility of the original peptide sequence (B1; EGGGFTVNWYFDV; SEQ ID NO:7) by removing the C-terminal Val residue and adding several charged residues at the N- as well as the C-terminal end of the peptide. The resulting peptides B1/4, B1/6 (acidic pI), B1/7 (basic pI) and their scrambled versions B1/5, B1/7scr3 are readily soluble in a variety of buffer systems at physiological pH.

Peptide	Sequence	Amino-acids	MW (D)	pI	Remark
B1	EGGGFTVNWYFDV ( <del>SEQ. ID. No. 44</del> ) (SEQ ID NO:7)	(13aa)	1491	6.0	Decreased solubility
B1/4	REGGGFTVNWYFDR ( <del>SEQ. ID. No. 45</del> ) (SEQ ID NO:45)	(14aa)	1704	7.9	Soluble,
B1/5	FGVGYRGETRNFWD ( <del>SEQ. ID. No. 46</del> ) (SEQ ID NO:46)	(14aa)	1704	8.0	Scrambled version, soluble
B1/6	EEEEGGGFTVNWYFDEEE ( <del>SEQ. ID. No. 47</del> ) (SEQ ID NO:47)	(18aa)	2166	5.0	Acidic pI soluble
B1/7	RRREGGGFTVNWYFDRRR ( <del>SEQ. ID. No. 48</del> ) (SEQ ID NO:48)	(18aa)	2329	9.9	Basic pI soluble
B1/7scr3	RRRFGVGYGETNFDWRRR ( <del>SEQ. ID. No. 49</del> ) (SEQ ID NO:49)	(18aa)	2329	9.9	Basic pI, soluble, scrambled version

Table 7 is a list of a series of antibody 198/B1 derived peptides. Listed are the length of the peptide (aa, amino acids #), the calculated molecular weight (MW, in Dalton (D) and the statistical isoelectric point (pI).--

Please cancel the present "SEQUENCE LISTING", pages 1-37, submitted November 1, 2001, and insert therefor the accompanying paper copy of the Substitute Sequence Listing, page numbers 1 to 42, at the end of the application.